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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	KUMAR *et al.*
U.S. Serial No.:	10/009,230
Filing Date:	05/17/2002
International Application No.:	PCT/IB00/00708
International Filing Date:	25 May 2000
For:	AMORPHOUS FORM OF FEXOFENADINE HYDROCHLORIDE

Box PCT
Assistant Commissioner of Patents
Washington, D.C. 20231

TRANSMISSION OF PRIORITY DOCUMENT

Applicants transmit herewith a certified copy of Indian Patent Application No. 776/Del/1999 25 May 1999 (25.05.1999) to which priority is claimed herein.

Respectfully submitted,

RANBAXY LABORATORIES LIMITED

By: _____
Jayadeep R. Deshmukh
Vice President - Intellectual Property

Dated: October 28, 2002

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INTELLECTUAL PROPERTY **INDIA**

GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY,
PATENT OFFICE, DELHI BRANCH,
W - 5, WEST PATEL NAGAR,
NEW DELHI - 110 008.

I, the undersigned, being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the Application, Complete Specification and Drawing Sheets filed in connection with Application for Patent No. ***776/Del/1999*** *dated* ***25th May 1999.***

Witness my hand this 17th day of October 2002.

(H.C. BAKSHI)
Deputy Controller of Patents & Designs.

FORM 1A

0776 DEL 99

THE PATENTS ACT, 1970

..AY 1999

25 MAY 1999

APPLICATION FOR PATENT

By the Assignee or Legal Representative of the True and First Inventor

(See Section 7)

(To be made in triplicate and shall be accompanied by three copies of the provisional specification in Form 3, or the complete specification in Form 34)

We, **RANBAXY LABORATORIES LIMITED**, a Company incorporated under the Companies Act, 1956 of 19, Nehru Place, New Delhi - 110 019, India hereby declare : -

(i) that we are in possession of an invention for **"PROCESS FOR THE PREPARATION OF NOVEL AMORPHOUS FORM OF FEXOFENADINE HYDROCHLORIDE"**

(ii) that we the said RANBAXY LABORATORIES LIMITED claim to be the assignee of or the legal representatives of :

Naresh Kumar, Chandrahas Khanduri and Mukesh Sharma of Ranbaxy Research Laboratories, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon - 122001, India, all Indian Nationals, and

who claim and are believed to be the true and first inventors thereof :

DUPLICATE

(iii) that the complete specification filed with this application is and any amended specification which may hereafter be filled in this behalf will be, true of the invention to which this application relates:

(iv) that we believe that we are entitled to a patent for the said invention having regard to the provisions of The Patents Act 1970s;

(v) that to the best of our knowledge, information and belief, the facts and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

We request that a patent may be granted to us for the said invention.

We request that all notices, requisitions and communications relating to this application may be sent to:

DR. BRIJ KHERA
Associate Director - Intellectual Property
Ranbaxy Laboratories Limited
Plot No. 20, Sector - 18,
Udyog Vihar Industrial Area,
Gurgaon - 122 001
Haryana, India

Dated this 7th day of May, 1999.

(Signature)

For RANBAXY LABORATORIES LTD.

Company Secretary

ENDORSEMENT BY THE TRUE AND FIRST INVENTORS

(i) **NARESH KUMAR**

(ii) **CHANDRAHAS KHANDURI**

(iii) **MUKESH SHARMA**

of Ranbaxy Laboratories Limited, Plot No. 20, Sector 18, Udyog Vihar Industrial Area, Gurgaon-122001 all Indian Nationals,

referred to on the reverse of this application as claiming to be the true and first inventors hereby declare that the applicant(s) who have signed this application on the reverse is / are / my / our assignee(s).

Dated this 7th day of May, 1999.

(i) Naresh Kumar

NARESH KUMAR

(ii)

CHANDRAHAS KHANDURI

(iii) Mukesh

MUKESH SHARMA

Two Witnesses :

1. G.V.R. Sharma

G.V.R. SHARMA

2.

MAHAVIR KHANNA

For RANBAXY LABORATORIES LTD.

Company Secretary

FORM 3 A

The Patents Act, 1970

COMPLETE SPECIFICATION
(See Section 10)

Duplicate

PROCESS FOR THE PREPARATION OF NOVEL AMORPHOUS FORM OF FEXOFENADINE HYDROCHLORIDE

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019

A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be perform d:

This invention relates to a process for the preparation of novel amorphous form of fexofenadine hydrochloride.

Chemically, fexofenadine is 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]-α, α-dimethylbenzene acetic acid also known as terfenadine carboxylic acid metabolite, having the Formula I as shown in the accompanied drawings. Fexofenadine hydrochloride (Terfenadine carboxylic acid hydrochloride) is an effective antihistamine which avoids adverse effects associated with the administration of terfenadine including abnormal heart rhythms in some patients with liver disease or who also take the antifungal drug ketoconazole or the antibiotic erythromycin.

The latest trend that has of late, crept into the pharmaceutical industry is the studies on polymorphism in drugs and the difference in the activity of different polymorphic forms of a given drug. By the term polymorphism we mean to include different physical forms, crystal forms, crystalline / liquid crystalline / non-crystalline (amorphous) forms. This has especially become very interesting after observing that many antibiotics, antibacterials, tranquilizers etc., exhibit polymorphism and some / one of the polymorphic forms of a given drug exhibit superior bio-availability and consequently show much higher activity compared to other polymorphs. It has also been disclosed that the amorphous forms in a number of drugs exhibit different dissolution characteristics and in some cases different bioavailability patterns compared to the crystalline form (Konne T., Chem. Pharm. Bull., 38, 2003 (1990). For some therapeutic indications one bioavailability pattern may be favoured over another. Sertraline, Frentizole, Sulphathiazole, Indomethacine etc. are some of the important examples of pharmaceuticals which exhibit polymorphism. Hosts of patents have been granted pertaining to these drugs. To cite a few, US Patent No. 5,248,699 discusses about five polymorphic forms of sertraline hydrochloride while EP 014590 describes four polymorphic forms of Frentizole. EP 490648 and EP 022527 also deal with the subject of polymorphism in drugs.

PCT Patent application WO 95/31437 discloses fexofenadine hydrochloride in various new crystalline forms designated Form I, Form II, Form III and Form IV and methods for their preparation.

The fact that amorphous form of fexofenadine hydrochloride has not been studied earlier coupled with the current interest in the field of polymorphism in drugs prompted us to take up this investigation.

It is an objective of the present invention to provide an efficient method for the preparation of new amorphous form of fexofenadine hydrochloride. The present process uses conditions which are convenient to operate on a commercial scale and operationally safe.

Accordingly, the present invention provides a process for the preparation of fexofenadine hydrochloride in an amorphous form which comprises dissolving crystalline fexofenadine hydrochloride in a suitable solvent or dissolving fexofenadine base in a suitable solvent and adding a suitable solvent containing hydrogen chloride and recovering amorphous form of fexofenadine hydrochloride from the solution thereof by spray drying or freeze drying technique.

In a preferred embodiment of the invention, fexofenadine hydrochloride is recovered from the solution in an amorphous form using a freeze drying technique. The freeze dryer (Model : Virtis Genesis SQ Freeze-Dryer), which is used operates on the principle of Lyophilization i.e. a process of stabilizing initially wet materials (aqueous solution or suspensions) by freezing them, then subliming the ice while simultaneously disrobing some of the bound moisture (primary drying). Following disappearance of the ice, disorption may be prolonged (secondary drying). This process is usually conducted under vacuum.

In a more preferred embodiment of the invention, fexofenadine hydrochloride is recovered from the solution in an amorphous form using a spray drying technique. The Mini-Spray Dryer (Model : Buchi 190, Switzerland) which is used, operates on the principle of nozzle spraying in an parallel - flow i.e. the sprayed product and the drying gas flow in the same direction. The drying gas can be air or inert gases such as nitrogen, orgon and carbon dioxide. Nitrogen is preferred in this case.

The term "suitable solvent" means lower alkanol or combination of lower alkanol and ester or ketone or chlorinated solvents. Lower alkanol includes those primary, secondary and tertiary alcohols having from one to six carbon atoms. Suitable lower alkanol solvents include methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, amyl alcohol

and t-butanol. The term ketone or ester includes solvents having from one to ten carbon atoms such as acetone, methyl ethyl ketone, 2-butanone, 4-methylpentan-2-one, ethyl acetate or n-butylacetate. The suitable chlorinated solvents include dichloromethane, chloroform or carbon tetrachloride. Mixture of these solvents is also contemplated.

Amorphous fexofenadine hydrochloride prepared according to the process of the present invention may be characterised by its infra-red spectrum in KBr disc (Figure 1) and by its X-ray powder diffraction pattern (Figure 2) as shown in the accompanied drawings. The infra red spectrum in KBr (Figure 1) obtained for the samples prepared by the process of the present invention is different than infra red spectrum in KBr for crystalline form (Figure 3) of fexofenadine hydrochloride obtained per WO patent application, as shown in the accompanied drawings. X-ray powder diffraction patterns gave a plain halo (Figure-2) and show no peaks which are characteristic of a crystalline fexofenadine hydrochloride (Figure-4) thus demonstrating the amorphous nature of the product.

The present invention is illustrated by the following examples, which are not intended to limit the effective scope of the claims.

EXAMPLE - 1

Preparation of amorphous fexofenadine hydrochloride by Spray Drying using crystalline fexofenadine hydrochloride

Fexofenadine hydrochloride crystalline (124 g) was dissolved in methanol (300 ml) at 25 - 30°C. The clear solution so obtained was subjected to spray drying in a Mini-Spray Dryer (Buchi Model 190) and fexofenadine hydrochloride in an amorphous form was isolated (114 g).

X-ray powder diffraction pattern (Figure 2, as shown in the accompanied drawings) shows a plain halo thus demonstrating the amorphous nature of the product. Infrared spectrum in KBr (Figure 1, .as shown in the accompanied drawings) is different than the one obtained for crystalline form of fexofenadine hydrochloride (Figure 3).

EXAMPLE - 2

The process of Example 1 was repeated with fexofenadine hydrochloride (10g) using ethylacetate (20 ml) and methanol (20 ml) instead of methanol to give amorphous fexofenadine hydrochloride (9.2g). IR (KBr) spectrum and x-ray crystallography confirmed that the material was amorphous in nature.

EXAMPLE - 3

The process of Example 1 was repeated with fexofenadine hydrochloride (10 g) using acetone (20 ml) and methanol (20 ml) instead of methanol to give amorphous fexofenadine hydrochloride (8.9 g). IR (KBr) spectrum and x-ray crystallography examination confirmed the amorphous nature of the product.

EXAMPLE - 4

Preparation of amorphous fexofenadine hydrochloride by spray drying using fexofenadine base.

Fexofenadine (15 g) was suspended in methanol (60ml) and to it was added isopropanol containing equivalent molar hydrogen chloride to get a clear solution. The clear solution was subjected to spray drying in a mini spray dryer (Buchi Model 190) and fexofenadine hydrochloride in an amorphous form was isolated (14.9 g). IR (KBr) and x-ray crystallography revealed that the product was amorphous.

EXAMPLE - 5

The process of Example 4 was repeated with fexofenadine (10g) using methanol (40ml) and methanol containing equimolar hydrogen chloride to give amorphous fexofenadine hydrochloride (9.5g). IR (KBr) spectrum and x-ray crystallography examination confirmed the amorphous nature of the product.

WE CLAIM:

1. A process for the preparation of fexofenadine hydrochloride in an amorphous form which comprises dissolving crystalline fexofenadine hydrochloride in suitable solvent(s) or dissolving fexofenadine base in a "suitable solvent(s) and adding suitable solvent containing hydrogen chloride and recovering fexofenadine hydrochloride from the said solution thereof by spray drying or freeze drying technique.

2. The process of claim 1 wherein suitable solvent means lower alkanol or combination of lower alkanol and ester or alkanol or ketone or chlorinated solvent.

3. The process of claim 2 wherein lower alkanol includes primary, secondary and tertiary alcohols having from one to six carbon atoms.

4. The process of claim 3 wherein the said lower alkanol is selected from the group consisting of methanol, ethanol, n-propanol, isopraponal or n-butanol or mixture thereof.

5. The process of claim 4 wherein the preferred solvent is methanol, ethanol or isopropanol.

6. The process of claim 2 wherein ester solvent is selected from ethyl acetate or n-butyl acetate.

7. The process of claim 2 wherein ketone solvent is acetone, methylethyl ketone, 2-butanone, 4-methyl pentan-2-one.

8. The process of claim 2 wherein chlorinated solvent is chloroform, dichloromethane or carbontetrachloride.

9. The process of claim 1 wherein fexofenadine hydrochloride in an amorphous form is isolated from the said solution by spray drying.

10. The process of claim 1 wherein the spray drying is effected in the presence of an inert gas.

11. The process of claim 1 wherein fexofenadine hydrochloride in an amorphous form is isolated from the said solution by freeze drying.

12. The process for the preparation of amorphous fexofenadine hydrochloride substantially as herein described and exemplified by the examples.

Dated this 11th day of May, 1999.

For Ranbaxy Laboratories Limited

(S. K. Patawari)
Company Secretary

Ranbaxy Laboratories Limited

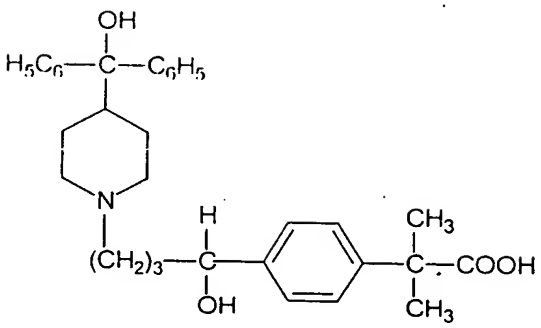
Application No.

No. of Sheets = 05

Sheet 01 of 05

0776 DEL 99

25 MAY 1999



Formula I

For Ranbaxy Laboratories Limited

(S. K. Patawari)
Company Secretary

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FIGURE - 1

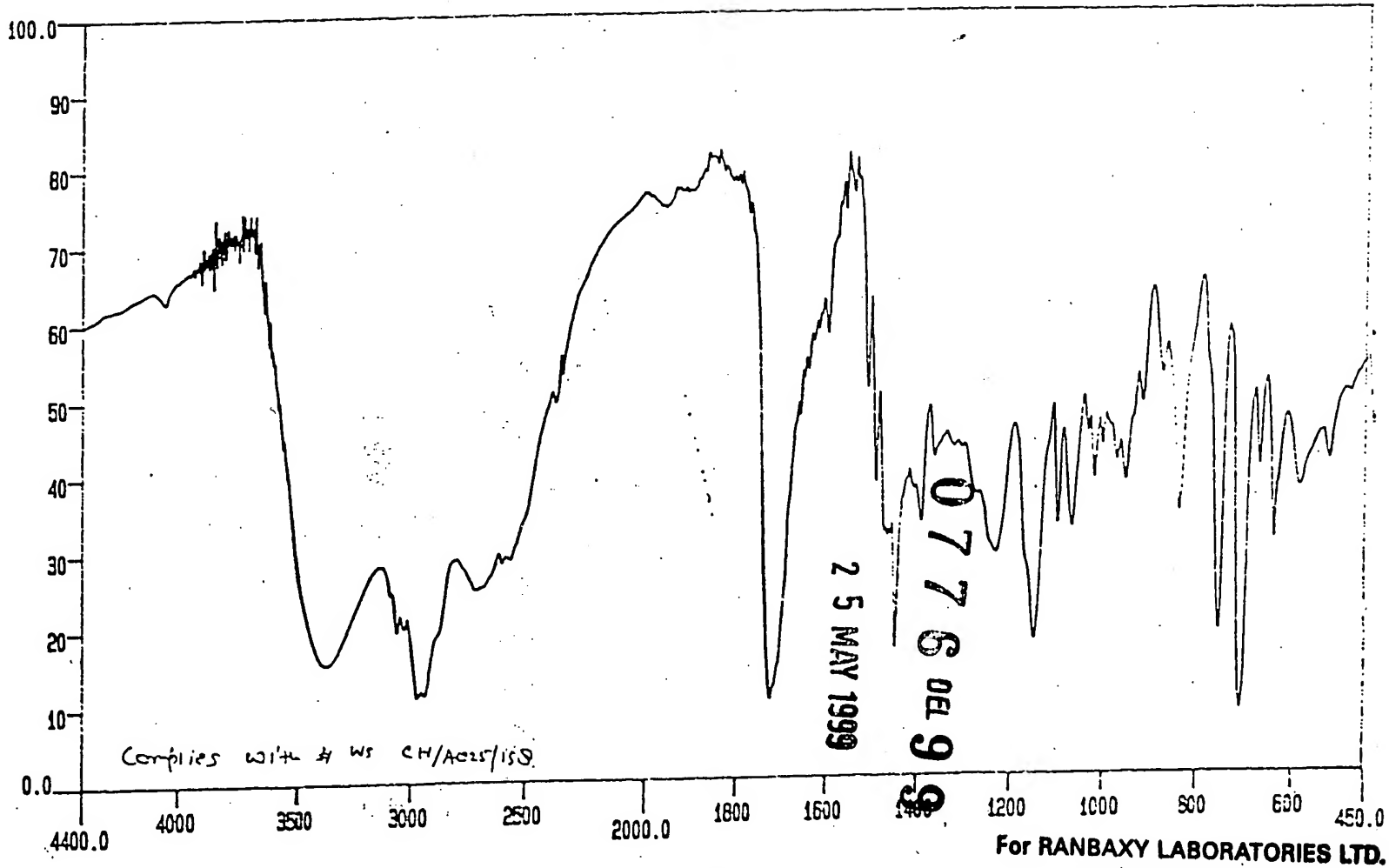

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FIGURE - 2

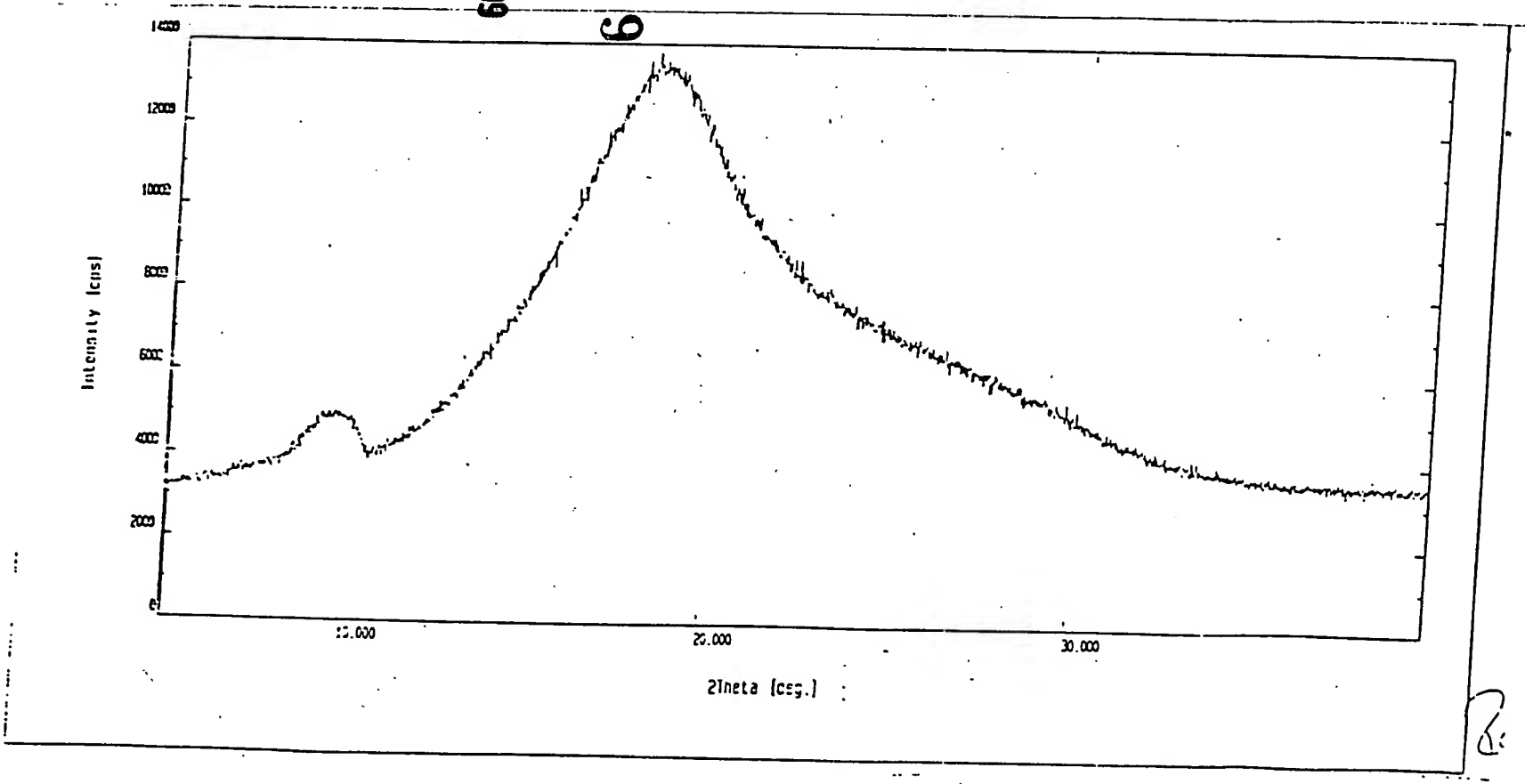

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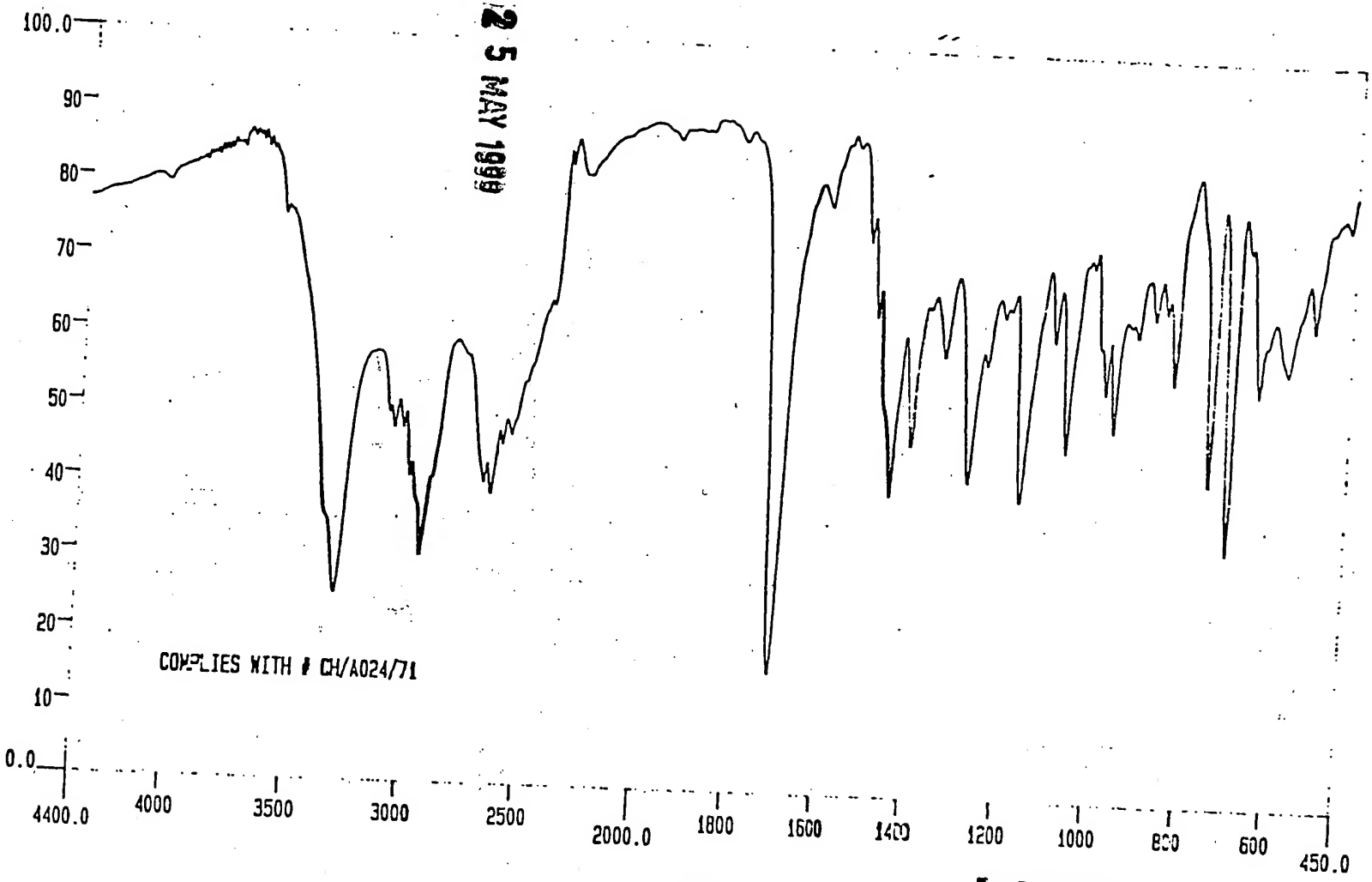
FIGURE - 3



25 MAY 1999

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FIGURE - 4